

## An unexpected circumstance; clozapine-induced amenorrhea: A case report

Clozapine-induced amenorrhea

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Most antipsychotic drugs employed in psychosis treatment can lead to amenorrhea and high prolactin levels in women. There are only a few studies on the overall impact of this adverse effect. Neglecting adverse effects of prescriptions in psychiatric follow-ups may cause loss of the sense of femininity, lack of birth control, and even premature menopause due to unrecognition of the menstrual cycle in women with psychosis. Clozapine is one of the antipsychotic drugs with the lowest accepted risk of hyperprolactinemia in therapeutic doses. Clozapine induced amenorrhea considered safe for hyperprolactinemia, is a rare condition. In the present study, we aimed to describe a clozapine-induced amenorrhea case and the clinical manifestation that improved with the alteration of aripiprazole treatment.

**Keywords**

Amenorrhea, Aripiprazole, Clozapine, Hyperprolactinemia

DOI: 10.4328/ACAM.20522 Received: 2021-02-05 Accepted: 2021-04-08 Published Online: 2021-11-15 Printed: 2022-03-15 Ann Clin Anal Med 2022;13(Suppl 1): S36-38

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## Introduction

Psychotropic drugs can lead to hyperprolactinemia due to D2 receptor obstruction in the anterior pituitary gland. As the binding rate of antipsychotic drugs to D2 receptors increases, their effects on the extrapyramidal system and the risk of high prolactin levels increase. Atypical antipsychotics have a lower potency D2 receptor antagonist effect when compared to conventional antipsychotics, and only moderately increase prolactin levels [1].

Hyperprolactinemia leads to menstrual cycle disorders such as oligomenorrhea and amenorrhea, galactorrhea, gynecomastia, sexual dysfunctions, and acne and hirsutism, weight gain, osteoporosis and mood changes in women. The frequency of endocrinological side effects due to high prolactin levels is 1-10% [2]. The rate of antipsychotic-induced hyperprolactinemia is reported between 60 and 75% in women and 34-43% in men [3].

It was accepted that clozapine, an atypical antipsychotic, does not increase plasma prolactin levels even at high doses, since it occupies D2 receptors at lower rates. There is no record of clozapine-induced amenorrhea in the literature. In the present case report, we aimed to discuss a schizophrenic patient who developed amenorrhea due to hyperprolactinemia after clozapine treatment and whose clinical manifestation improved with the alteration of aripiprazole treatment.

## Case Report

The initial complaints of a 36-year-old, single, primary school graduate female patient started about 15 years ago as nervousness, aggression, suspiciousness, insomnia, introversion, hearing voices and soliloquy. The patient, diagnosed with schizophrenia during several hospitalizations and regular psychiatric follow-ups, applied to the gynecology and obstetrics outpatient clinic due to amenorrhea. No gynecological organic pathology was determined, additional hormonal treatment was not recommended, and the patient was referred to the psychiatry outpatient clinic. The patient, who had no active psychological complaints and has been using 200 mg/day clozapine regularly for the last six months, had not had a period during the last 3 months. She used olanzapine, risperidone, amisulpride, and quetiapine-based frugs during the inpatient and outpatient periods; however, she benefited significantly from the last clozapine treatment.

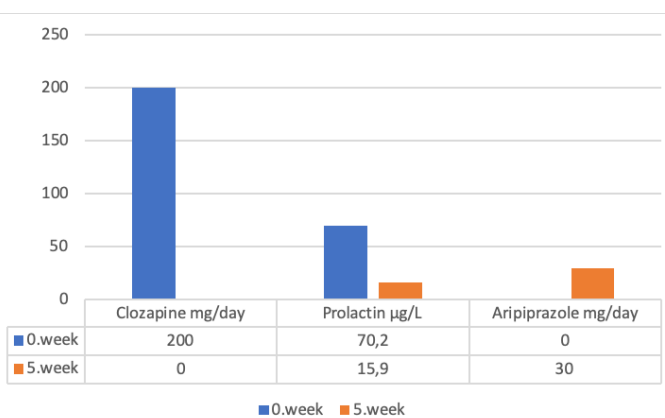
In the psychological examination, the patient was determined as conscious, cooperative, oriented, good self-care, with an appearance compatible with her age, and limited eye contact. There were no pathological perception symptoms. Memory and intelligence level were normal. Her affection was obtuse, her associations were regular, abstract thinking skills, ability to evaluate reality, and her attention to detail was full. It was observed that her affection was consistent with her mood, and her mood was depressive. Her speech was slow, and her speech style was normal. Reference ideas were continuous in her thought content. Her sleep was normal. The patient who was without active positive symptoms and with a positive and negative syndrome subscale score of 15 in the Positive and Negative Syndrome Scale (PANSS) and the general psychopathology subscale score of 21, was considered in

remission.

She had no history of alcohol or substance use, concomitant organic disease, known drug allergy or drug use. The patient did not have a partner or a regular sex life. She lived alone. In her family, two aunts were diagnosed with bipolar disorder.

General neurological and physical examination findings were normal, and no unusual weight gain or hair growth was observed. She did not have breast fluid discharge, breast tenderness or swelling, and lack of sexual desire complaints. No specificity was found in the complete blood count and routine biochemistry tests requested for the patient. The beta-hcg level was zero and the fasting prolactin level was 70.2 µg/L. The patient was referred to our clinic from the obstetrics and gynecology department, after organic pathologies were excluded, and after endocrinology department consultation for possible pituitary pathologies. Since endocrinology did not identify anomalies in other hormone levels in the contrast-enhanced and non-contrast pituitary magnetic resonance imaging (MRI), alteration of the antipsychotic treatment was recommended initially. Hyperprolactinemia due to clozapine administration was considered, and the patient was crossed over from clozapine to aripiprazole.

The clozapine dose of 200 mg/day was gradually decreased and discontinued, aripiprazole 10 mg/day was prescribed, and the dose was gradually increased to 30 mg/day. The patient, whose psychological complaints did not increase during the psychiatry outpatient clinic follow-ups, started to menstruate in the fourth week of aripiprazole treatment. After the regular weekly endocrinology outpatient controls, the patient's prolactin level was measured as 15.03 µg/L at the fifth week of the new treatment (Figure 1). The patient did not have any psychological or physical complaints during the next three months of the outpatient clinic follow-up, and prolactin levels remained within normal limits. The patient was monitored by the endocrinology department and monthly by the psychiatry outpatient clinic and continued the current treatment.



**Figure 1.** Prolactin and antipsychotic drugs levels

## Discussion

It is known that atypical antipsychotic drugs increase prolactin levels less than typical antipsychotics [1]. Clozapine is a second-generation antipsychotic with effects on dopamine, serotonin, histamine receptors and muscarinic, glutamatergic and adrenergic receptors. Clozapine is one of the most effective treatment methods for schizophrenia [1].

Hyperprolactinemia is an adverse effect that could develop during the use of typical and atypical antipsychotics leading to dopaminergic obstruction in the hypothalamic-pituitary-gonadal axis. If hyperprolactinemia is observed, detailed blood tests should be conducted, in addition to anamnesis, physical examination, and a pregnancy test. The presence of complaints such as headache and visual impairment in the history should suggest an intracranial mass. However, the absence of such complaints does not exclude central nervous system pathologies. Thus, the patient should be referred to an endocrinologist for further examination and imaging [4]. Since it is known that the prolactin levels after antipsychotic use are at most 150 ng/ml, this would assist the etiology.

Clozapine is one of the antipsychotic drugs with the lowest accepted risk of hyperprolactinemia in therapeutic doses. It was even observed that clozapine decreased prolactin levels in patients with treatment-induced hyperprolactinemia. However, although the risk of hyperprolactinemia was higher during the periods when our patient took risperidone and amisulpride, hyperprolactinemia-induced amenorrhea was not observed, and the most interesting fact about our case was that amenorrhea was observed after clozapine treatment. This may suggest that hyperprolactinemia in our patient may be observed due to genetic differences in the receptors on which clozapine is effective; however, nothing definitive could be argued since no genetic analysis was conducted.

Although certain studies reported that stable patients with amenorrhea respond better to D2 receptor agonists, the drug treatment was changed in our patient due to the possibility of psychotic exacerbation that may develop with the addition of D2 receptor agonists to the treatment without changing the antipsychotic [5].

There are case reports and studies which indicated that adding aripiprazole to the treatment in the case of antipsychotic-induced hyperprolactinemia leads to a reduction in prolactin levels [6]. Aripiprazole treatment was attempted in the patient based on the knowledge that aripiprazole reduced the symptomatic hyperprolactinemia effects of other antipsychotic drugs [7,8]. In our case, we supported this knowledge by switching to aripiprazole treatment and observed that the amenorrhea manifestation improved after the switch.

### Conclusion

During hyperprolactinemia diagnosis, initially all hyperprolactinemia factors other than antipsychotic treatment should be excluded. Aripiprazole with a partial agonist action mechanism and strong affinity to bind to D2 receptors, could provide an alternative treatment to help reduce hyperprolactinemia [8]. The present case emphasized that the possible side effects of drugs should be questioned regardless of the associated risks. Although it is a rare condition, it should be kept in mind that amenorrhea may develop due to hyperprolactinemia in a group of patients after clozapine initiation. We must remember that sometimes the least expected drugs could cause surprising adverse effects.

### Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

### Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

### Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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### How to cite this article:

Aslı Kazgan, Sevler Yıldız. An unexpected circumstance; clozapine-induced amenorrhea: A case report. *Ann Clin Anal Med* 2022;13(Suppl 1): S36-38